SOME HYDANTOIN DERIVATIVES.

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Mendel and Dakin were the first to emphasize the fact that the generally accepted structural formula for allantoin contained an asymmetric carbon atom, and, because of this, should be capable of existing in two stereoisomeric forms. However, all attempts to resolve allantoin into its optically active components have failed. On the basis of this, Dakin formulated a structure for allantoin which may be regarded as a tautomeric form to the one generally accepted. Dakin further carried his analysis to substituted hydantoins and discovered the peculiar behavior of the optically active hydantoins towards alkali, which results in the formation of inactive forms. This reaction is remarkable in that the racemization proceeds with a much greater velocity than that observed for other substances. On the other hand, methylethylhydantoin could not be racemized.

Dakin has also made the observation that optically active amino-acids give rise to optically active hydantoins. This observation seems to be of considerable interest in connection with Dakin's theory of the structure of hydantoins. Since the active forms of the amino-acids give rise to active hydantoins, it is logical to assume that the dl forms of amino-acids, when first converted into hydantoins, should consist of a mixture of the d and the l forms. Further, it is logical to assume that substances consisting of such mixtures should differ in their physical properties from their tautomeric forms. It seemed of interest, therefore, to compare the physical properties—such as melting point, crystal form, refractive index—of the dl hydantoins and the hydantoins inactiv-

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ated by alkali. Had such differences been found, Dakin's theory would have received additional support. This consideration prompted the undertaking of the present investigation some years ago. It was found, however, that both the inactivated and the dl forms, in the majority of instances, did not differ in their melting points, and, roughly, in their crystal forms. At this time, it is impossible to undertake the work on the refractive indices and the work has been abandoned. It is published in its present form because of the additional data it contains on various hydantoins earlier described and because of the new hydantoins prepared during the course of this work.

Melting point.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Given °C</th>
<th>Found °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydantoin acid</td>
<td>155, 160</td>
<td>179-180</td>
</tr>
<tr>
<td>dl-Methylhydantoin</td>
<td>150</td>
<td>155-156</td>
</tr>
<tr>
<td>dl-α-Phenyleiroidopropionic acid</td>
<td>168, 170</td>
<td>174</td>
</tr>
<tr>
<td>dl-α-Phenylmethylhydantoin</td>
<td>172, 173</td>
<td>178</td>
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<tr>
<td>d-α-Phenyleiroidopropionic acid</td>
<td>175</td>
<td>178</td>
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<tr>
<td>d-α-Phenylmethylhydantoin</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>d-α-Naphthyleiroidopropionic acid</td>
<td>198-200</td>
<td>166</td>
</tr>
<tr>
<td>d-α-Naphthylmethylhydantoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated napththylmethylhydantoin</td>
<td>179-180</td>
<td></td>
</tr>
<tr>
<td>a-Ureido butyric acid</td>
<td></td>
<td>184</td>
</tr>
<tr>
<td>Ureidodimethylacetic acid</td>
<td>160</td>
<td>184</td>
</tr>
<tr>
<td>dl-Hydantoic acid acetic acid</td>
<td>214, 225</td>
<td>228-229</td>
</tr>
<tr>
<td>d-Hydantoic acid propionic acid</td>
<td>179, 180</td>
<td>179-180</td>
</tr>
<tr>
<td>dl-Hydantoic acid propionic &quot;</td>
<td>167-169, 165</td>
<td>179-180</td>
</tr>
<tr>
<td>Inactivated hydantoic acid propionic acid</td>
<td>167-169</td>
<td>177-178</td>
</tr>
<tr>
<td>dl-γ-Hydroxybenzylhydantoin</td>
<td>158-160</td>
<td>158-160</td>
</tr>
<tr>
<td>Inactivated benzylhydantoin</td>
<td>158-160</td>
<td>158-160</td>
</tr>
<tr>
<td>t-Hydroxybenzylhydantoin</td>
<td>158-160</td>
<td>158-160</td>
</tr>
</tbody>
</table>

EXPERIMENTAL.

Hydantoic Acid.—7.5 gm. of glycocoll, 8.1 gm. of potassium cyanate, and 20 cc. of water were heated on the water bath for 1 hour. The solution was filtered and concentrated hydrochloric acid added until the reaction was acid to Congo red. The acid which separated out on cooling was recrystallized from boiling water. Hydantoic acid decomposes at 179-180° (uncorrected); Diels and Heintzel\(^4\) give the decomposition point at 155°, Weidel and Roithner\(^5\) as 153-154°, Griefs\(^6\) as 160°.

Hydantoin.—Hydantoin was prepared according to the two methods of Harries and Weiss and their later statement, that the two products were identical, was confirmed. The melting point was found to be 218–220°, as given by Tafel and Reindl.

Calculated for $C_3H_6O_2N_2$..........................N 28.00
Found.................................................N 27.80 27.82

$dl$-$\alpha$-Methylhydantoin.—6 gm. of $dl$-$\alpha$-ureidopropionic acid and 50 cc. of 10 per cent hydrochloric acid were boiled for 2 hours and the resulting solution was concentrated to a small volume. The $dl$-$\alpha$-methylhydantoin which crystallized out melted at 155–156° after one recrystallization. Dakin found the melting point to be 150°.

Calculated for $C_3H_6O_2N_2$..........................N 24.60
Found.................................................N 24.47

$dl$-$\alpha$-Phenylureidopropionic Acid.—This acid was prepared by shaking 5 gm. of $dl$-$\alpha$-ureidopropionic acid with 6.5 gm. of phenylisocyanate for 2 hours. The diphenylurea was filtered off and the solution acidified with dilute hydrochloric acid. The insoluble phenylureidopropionic acid separates out at once and may be recrystallized from a large volume of boiling water. $dl$-$\alpha$-Phenylureidopropionic acid forms small iridescent plates which melt at 174° with decomposition. Kühn gives the melting point as 170°, Paal as 168°.

Calculated for $C_{16}H_{16}O_2N_2$..........................N 13.46
Found.................................................N 13.47

$dl$-$\alpha$-Phenylmethylhydantoin.—When the above ureido acid is heated with 20 per cent hydrochloric acid for 1 hour, it yields $dl$-$\alpha$-phenylmethylhydantoin. Upon cooling the solution, the hydantoin crystallizes in long, silky needles which melt at 178°. Recrystallization from water did not change the melting point. Mouneyrat gives the melting point at 172–173°.

Calculated for $C_{16}H_{16}O_2N_2$..........................N 14.74
Found.................................................N 14.94

$d$-$\alpha$-Phenylureidopropionic Acid.—This acid was prepared in the same way as the inactive compound. Recrystallized from boiling water, it forms small silky needles which melt at 175° with decomposition.

7 Harries, C., and Weiss, M., Ber. chem. Ges., 1900, xxxiii, 3418.
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0.1000 gm. substance neutralized 9.67 cc. 0.1 N HCl.
Calculated for C_{10}H_{12}O_{2}N_{2}................................. N 13.46
Found................................................. N 13.54

Rotation:

0.2741 gm. substance in 5.9286 gm. acetone gave a value for \([\alpha]\) of +0.18°.

\[
[\alpha]^0_b = \frac{5.9286 \times 0.18^\circ}{0.2741 \times 0.5} = + 7.78^\circ
\]

\(dL-\alpha\)-Phenylmethylhydantoin.—Prepared by boiling the ureido acid with 20 per cent hydrochloric acid, the hydantoin crystallized from the hot acid solution in short pointed silky needles, which melt sharply at 178°. The melting point was not changed on recrystallization.

0.1000 gm. substance neutralized 10.37 cc. 0.1 N HCl.
Calculated for C_{10}H_{12}O_{2}N................................. N 14.74
Found................................................. N 14.51

Rotation:

0.2700 gm. substance in 5.0410 gm. 0.5 N sodium hydroxide gave a value for \([\alpha]\) of +0.06°.

0.2031 gm. substance in 5.0988 gm. acetone gave a value for \([\alpha]\) of −0.20°.

\[
[\alpha]^0_b = \frac{5.0410 \times 0.06^\circ}{0.2700 \times 0.5} = + 2.24^\circ \text{ (sodium hydroxide)}.
\]

\[
[\alpha]^0_b = \frac{5.0988 \times -0.20^\circ}{0.2031 \times 0.5} = - 10.04^\circ \text{ (acetone)}.
\]

\(dl-\alpha\)-Naphthylmethylhydantoin.—Inactive \(\alpha\)-naphthylureidopropionic acid\(^{13,14}\) was boiled with a large excess of 20 per cent hydrochloric acid for 1 hour. A small part of the reaction product was in solution at the end and separated in long silky needles upon cooling. Most of the hydantoin, however, was in the form of an oil at the bottom of the flask and quickly solidified. Naphthylmethylhydantoin is very insoluble in boiling water but may be easily recrystallized from dilute alcohol. It melts at 179–180°.

0.1000 gm. substance neutralized 8.51 cc. 0.1 N HCl.
Calculated for C_{10}H_{12}O_{2}N................................. N 12.07
Found................................................. N 11.91

\(^{13}\) Neuberg, C., and Rosenberg, E., Biochem. Z., 1907, v, 456.

d-α-Naphthylureidopropionic Acid.—5 gm. of alanine, 10 gm. of naphthylisocyanate, and 20 cc. of 10 per cent sodium hydroxide were shaken for several hours, the reaction product was filtered, and the filtrate acidified with dilute hydrochloric acid. The acid separates at once and may be recrystallized from a large volume of boiling water or from dilute alcohol. It forms short needles, which melt at 198–200° with decomposition.

0.1000 gm. substance neutralized 7.8 cc. 0.1 N HCl.

Calculated for C₁₁H₁₂O₄N₃..............................N 11.20
Found.................................................N 10.95

Rotation:

0.1900 gm. substance in 7.229 gm. 0.5 N sodium hydroxide gave a value for [α] of +0.05°.

\[
[\alpha]_D = \frac{7.229 \times 0.05°}{0.1900 \times 0.5} = +3.80°
\]

d-α-Naphthylmethylhydantoin.—Prepared in the same way as the inactive compound and recrystallized from boiling water or dilute alcohol, the hydantoin melts at 166°. Repeated crystallization did not raise the melting point. The inactive ureido acid crystallizes very well from 95 per cent alcohol.

0.1000 gm. substance neutralized 8.51 cc. 0.1 N HCl.

Calculated for C₁₁H₁₂O₂N₂..............................N 12.07
Found.................................................N 11.91

Rotation:

0.2504 gm. substance in 5.2367 gm. acetone gave a value for [α] of −0.42°.

\[
[\alpha]_D = \frac{5.2367 \times -0.42°}{0.2504 \times 0.5} = -17.83°
\]

Two attempts were made to inactivate this hydantoin with normal sodium hydroxide. The first consisted in allowing the hydantoin to stand with an excess of sodium hydroxide for 2 days. At that time the rotation was zero. Because part of the compound was in the form of the sodium salt, it was warmed on the water bath before acidifying. The product which separated proved to be the inactive naphthylureidopropionic acid, decomposing at 199–200°, and yielded, when heated with 20 per cent...
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hydrochloric acid, the inactive hydantoin, melting at 179-180°. In the second experiment the heating on the water bath was omitted but the result was the same, the dl-ureido acid. Lack of material prevented the testing of a weaker alkali or of a shorter time of inactivation.

α-Ureidobutyric Acid.—10 gm. of α-aminobutyric acid, 8 gm. of potassium cyanate, and 25 cc. of water were heated 1.5 hours on a boiling water bath. The product which separated out on acidification melted, with decomposition, at 184°, both before and after crystallization from boiling water.

0.1000 gm. substance neutralized 13.0 cc. 0.1 N HCl.
Calculated for C₅H₁₀O₃N₂.......................... N 19.30
Found ........................................ N 19.32

Heated 1 hour with 10 per cent hydrochloric acid, the above acid gave α-ethylhydantoin, melting at 121-122°. Koenigs and Mylo⁵ found 118-120°.

Ureidodimethy lacetic Acid.—10.3 gm. of α-aminoisobutyric acid, 8.1 gm. of potassium cyanate, and 25 cc. of water were heated on the water bath 1.5 hours and then acidified with concentrated hydrochloric acid. Twice recrystallized from boiling water, in which it is fairly insoluble, the acid melts at 184° with decomposition. Urech⁶ gives the decomposition point as 160° and states that it is rather easily soluble in water.

Calculated for C₅H₁₀O₃N₂.......................... N 19.30
Found ........................................ N 19.08

Upon heating 1.5 hours with 10 per cent hydrochloric acid, the acid forms α-dimethylhydantoin, which melts at 175-176° as given by Urech and by Heipern.⁷

Calculated for C₅H₁₂O₂N₂.......................... N 21.87
Found ........................................ N 21.73

p-Hydroxybenzylhydantoin.—The hydantoin from dl-tyrosine (Kahlbaum) and from active tyrosine were prepared according to

the directions of Dakin\textsuperscript{18} and the properties as given by him confirmed.

The active compound was then inactivated by allowing a solution in N sodium hydroxide to stand about 24 hours. Uponacidification and recrystallization of the inactivated hydantoin from boiling water, it forms prisms of the same appearance as the dl-hydantoin, and not plates, as observed by Dakin. The melting points of the three forms, the dl, the d, and the inactivated, were the same, 158–160°, as given by Dakin.

dl-Hydantoinacetic Acid.—5 gm. of aspartic acid, 6 gm. of potassium cyanate, and 25 cc. of water were heated about 5 hours on a water bath. The resulting sirup was taken up in 10 per cent hydrochloric acid, boiled for 15 minutes, and the solution concentrated to dryness. Twice recrystallized from a little water it melts at 228–229° with decomposition. Dakin\textsuperscript{19} gives the melting point of the inactive compound, obtained by the action of alkali upon the active acid, as 225–228°. Johnson and Guest,\textsuperscript{20} who prepared it by the action of chloroacetic acid upon 2-thiohydantoin-4-acetic acid, give the melting point as 214–215°.

\begin{align*}
\text{Calculated for } & \text{C}_8\text{H}_{12}\text{O}_2\text{N}_4: \quad \text{N} & = 17.70 \\
\text{Found:} \quad & \text{N} & = 17.51
\end{align*}

dl-Hydantoinpropionic Acid.—10 gm. of dl-glutamic acid, 7 gm. of potassium cyanate, and 25 cc. of water were heated on a water bath for several hours until a thick sirup resulted. This was then taken up in an excess 10 per cent hydrochloric acid and boiled 20 minutes. The reaction product was evaporated to dryness in vacuum and the residue recrystallized twice from water. The acid melted at 179–180°. A second preparation showed the same melting point. Dakin\textsuperscript{21} gives the melting point of the inactive product obtained by racemization of the active acid as 167–169°. Johnson and Guest\textsuperscript{22} prepared the acid by desulfurizing the thiohydantoin and found the melting point to be 165°.

\textsuperscript{18} Dakin, \textit{Am. Chem. J.}, 1910, xliv, 55. \\
\textsuperscript{19} Dakin, \textit{Am. Chem. J.}, 1910, xliv, 58. \\
\textsuperscript{20} Johnson, T. B., and Guest, H. H., \textit{Am. Chem. J.}, 1912, xlviii, 109. \\
\textsuperscript{21} Dakin, \textit{Am. Chem. J.}, 1910, xliv, 59. \\
\textsuperscript{22} Johnson and Guest, \textit{Am. Chem. J.}, 1912, xlvii, 249.
The active acid melted at 179–180° as given by Dakin.

0.2160 gm. substance in 5.2593 gm. 0.5 N sodium hydroxide gave a value for \([\alpha]\) of \(-1.65^\circ\) in a 0.5 dm. tube.

\[
[\alpha]_0 = \frac{5.2593 \times -1.65^\circ}{0.2160 \times 0.5} = -80.30^\circ
\]

During the course of 6 hours this value fell from \(-1.65^\circ\) to \(-1.32^\circ\). The rate of inactivation is much more rapid in \(n\) sodium hydroxide (Dakin). The melting point of this substance was found by Dakin to be 167–169°. Crystallized from water, the melting point was found to be 177–178°.
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